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Letter to the Editor

Cytisine as an Emerging Tool for Smoking Cessation and Addiction Treatment

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Dear Editor-in-Chief

Cytisine as a plant-based alkaloid derived from Cytisus laburnum, or Golden Rain acacia, is a highly promising smoking-cessation tool that has been at the forefront of research lately. Investigations into its pharmacological characteristics and therapeutic potential place this compound as a strong competitor to existing anti-smoking drugs, such as varenicline, in addition to the traditional nicotine replacement therapies (1-4). This letter focuses on the main characteristics of cytisine: its toxicity, comparative benefits, efficacy, and potential applications in therapies against addiction.

Cytisine represents a partial agonist of the nicotinic acetylcholine receptors, specifically in the α4β2 subtype, thereby playing a critical role in the reward networks of nicotine addiction within the brain. Hence, cytisine as a medication partially activates these respective receptors in patients seeking to quit smoking and attenuates cravings and withdrawal symptoms. There is some similarity in the mechanism of action compared with varenicline except for some pharmacokinetic differences, which might explain the differing adverse effect profile of the drug (1).

A cytisine-containing medication was tested in several randomized controlled trials, which established its efficacy for smoking cessation (2). One large-scale study reported that the use of cytisine significantly increases quit rates when compared with a placebo, 2-fold or more. Cytisine had equal efficacy to the first-line pharmacologic treatment of nicotine addiction, varenicline, with a quit rate of approximately 22% at six months, comparable to rates reported for varenicline (3,4). Another pilot study New Zealand reported that cytisine was more efficacious than NRT in inducing higher rates of abstinence sustained up to six months (4).

The adverse events associated with cytisine therapy must be put into consideration in the evaluation of safety profile associated with cytisine therapy. Digestive adverse effects, including nausea and vomiting, were reported in up to 8.4% of patients treated with cytisine (5). Other serious psychiatric adverse effects have been reported, such as anxiety and psychosis, but the symptoms appeared to be resolved after drug discontinuation (1,6). Certain cases of allergic reactions, including urticaria, have been noted (7). Headache, dry mouth, constipation, sleeplessness, mildly increased blood pressure, and disturbances of the sleep pattern were described as common adverse effects in patients receiving cytisine (1,6,7). Some have also reported cardiovascular adverse effects, such as palpitations and slight increases in blood pressure, in addition to skin reactions like rash

and pruritus in some patients (7). Despite these adverse effects, the overall safety profile for cytisine is considered good; most adverse events are minor and transitory (8).

Studies into the toxicity of cytisine, particularly in comparison with nicotine, have mostly served to support its superior safety record. Non-toxic levels of cytisine in zebrafish models counteract the very negative consequences of nicotine, such as mortality and anatomical alterations including spinal curvature and pericardial edema (1,4). Further, nicotine produced a much greater embryotoxicity at lower doses in the zebrafish embryos; concurrently, cytisine itself did not demonstrate significant death or developmental abnormalities (2). Similarly, human studies also confirmed general cytisine safety; during the performance of clinical trials, the most commonly reported side effects were mild to moderate gastrointestinal disturbances and sleep disorders, and there was no evidence of an increase in the number of major adverse events attributed to cytisine administration (1, 3).

Cytisine is purported to have additional applications in the treatment of addictions other than nicotine addiction. Cytisine may play a role in controlling the amount of ethanol consumed and related neurochemical alterations. For instance, cytisine can influence the ethanol-induced alterations in the brain, suggesting a potential function for cytisine in the treatment of alcohol use disorders. According to these results, cytisine can be used more widely to treat addiction, although more research is needed to confirm its safety and effectiveness in various contexts (3).

Cytisine is well and rapidly absorbed and, subsequently, cleared in patients, with a mean half-life of approximately 4.8 hours. For this reason, based on this profile of pharmacokinetics, repeated dosing is required to maintain effective plasma concentrations of cytisine—up to once every two to three hours. The usual dose for smoking cessation is a tapering regimen spread over 25 days; six tablets per day are taken during the first three days of treatment, and one tablet per day at the end of it (3).

Cytisine is an exciting smoking-cessation therapy because of its safe, inexpensive, and effective combination. Its versatility as a pharmacotherapeutic drug can be seen also in its prospective use for the treatment of different kinds of addiction. If further research supports its application, cytisine could become one of the pillars of therapy for nicotine addiction and even other substance use disorders.

Conflict of Interest

Non-declared.

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